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REPORT
CD NO.

50X1-HUM

COUNTRY	USSR
SUBJECT	Scientific - Medicine, virus diseases
HOW PUBLISHED	Bimonthly periodical
WHERE PUBLISHED	Moscow
DATE PUBLISHED	May 1951 (delayed)
LANGUAGE	Russian
DATE OF INFORMATION	1951
DATE DIST.	23 May 1952
NO. OF PAGES	5
SUPPLEMENT TO REPORT NO.	

THIS IS UNEVALUATED INFORMATION

SOURCE Nevropatologiya i Psikhiatriya, Vol XX, No 2, 1951, pp 56-60.

CLINICAL ASPECTS AND HISTOPATHOLOGY OF A DISEASE OF HEMORRHAGIC FEVER TYPE IN BUKOVINA

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In the summers of 1947 and 1948, a considerable number of cases of infections of a general fever type were observed in the forest regions of Bukovina. These cases exhibited a general hemorrhagic syndrome, as well as considerable involvement of the nervous system. In the majority of cases, sojourn in the woods and tick bites preceded the infection, so that a virus etiology of the disease could be suspected. This suspicion was confirmed by neurological and virusological institutes.

While the clinical picture, pathomorphological data, and results of virusological investigations show close resemblances to the so-called hemorrhagic fevers (Crimea or Omsk hemorrhagic fevers), the disease still has clinical and pathomorphological peculiarities which permit it to be classified as a separate entity, i. e., the Bukovina hemorrhagic fever.

Clinically, the disease is characterized by uninterrupted fever for 7 days, acute general weakness, pains in the waist and muscles of the calf, headache, loss of consciousness; there were also hyperemia of the face, congestion of scleral vessels, slight swelling of the face and brows, subicteric state of the sclera, hyperemia of the throat, hemorrhagic rashes of various localization and types, weakly defined tendency towards bleeding of the gums and of the mucous membranes of the mouth, and, in some cases, bleeding from the nose and bruises on various parts of the skin. In some cases, the pulse lagged behind the temperature and there were bradycardia and lowering of the blood pressure.

The blood composition showed characteristic changes. During the first days, there was leukocytosis which often changed into leukopenia; furthermore, a pronounced shift to the left at the expense of the rod-shaped forms and monocytes was observed. This was accompanied by an increase in the number of lymphocytes. In some cases, young forms, myelocytes, and Tuerk's irritation cells were present. In a number of cases, thrombopenia was noted.

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In order to carry out a complete clinical investigation of hemorrhagic fever on our patients, we studied the clinical aspects of the afflictions of the nervous system in this disease and, in the course of this study, came to the conclusion that the neurological syndrome is often in the forefront in this disease, in many cases becoming predominant.

Symptoms of affliction of the somatic and vegetative nervous system which were more or less pronounced were detected in all patients examined in the acute fever period, as well as during convalescence.

We investigated 26 hemorrhagic fever patients in the summer of 1947 and ten patients in 1948.

According to the degree of affliction of the nervous system, the cases may be classified as follows:

Group 1. Acute disease with a lethal outcome, accompanied by diffuse meningoencephalytis with extensive participation of the cortex, subcortical nodes, and the stem (eight cases).

Group 2. Disease ending in recovery, but patients exhibiting appreciable cerebral symptoms expressed in the presence of an ataxia syndrome, extrapyramidal pathology, and changes of the psyche (three cases).

Group 3. Disease of a medium degree of severity. Patients in the fever stage showed meningeal symptoms, were in a stunned state, exhibited slight stem and pyramidal symptoms; during the period of convalescence, these symptoms disappeared almost completely, leaving only slight residual traces (13 cases).

Group 4. A light form of the disease without meningeal symptoms. However, neurological examination of the patients still disclosed symptoms of affliction of the nervous system, radiculo-[illegible]ic symptoms, and phenomena of vegetative dystonia.

[Case histories and clinical symptoms of three typical cases, belonging to groups 1, 2, and 3 respectively, are described by the authors in detail, in order to illustrate the following text.]

In cases of Group 1, the disease set in very rapidly, without preliminary symptoms, and reached its culmination on the second and third day. Primary symptoms comprised fever, headache, pains in the waist, and muscle pains in the legs. Vomiting was often observed on the first or second day. The temperature immediately reached a high level and remained on that level. In all cases, there were more or less pronounced symptoms of a hemorrhagic syndrome. Extensive nasal, gastro-intestinal, pulmonary, and other hemorrhages of the type observed in Crimean hemorrhagic fever and infectious nephroso-nephritis were absent. The following changes of internal organs were observed: the tongue was usually dry, with a white or brown film; a tenuous pulse, occasionally accelerated, often lagging behind the temperature, bradycardia, lowered blood pressure, urination unaffected, blood showing the characteristic changes mentioned above.

In addition to general infection symptoms, changes of consciousness appeared on the second and never later than the fourth day. These included stupor, amential-delirious [illegible]drome, sopor, and coma. There was a rapid transition from stupor to sopor. In [illegible] cases, there were symptoms of psychomotor excitement accompanied by disconnected delirium, hallucinations, and attempts to get up and run somewhere. These symptoms most frequently appeared at night; during the day, a completely passive state predominated.

Since the first day of the disease, meningeal symptoms were observed. Among them were rigidity of the back of the neck, symptom of Kernig and Brudzinskiy, and a meningeal position (head thrown back, bent lower extremities, abdomen pulled in). Affection of nerves of the large brain was not sharply expressed in patients of this group. It mainly involved the oculomotor group, so that anisocoria, miosis, and mono- and bilateral ptosis were observed. In two cases, a well-expressed Claude Bernard - Gorner symptom of brain stem origin was observed. Among other nerves, the sublingual [lingual] and glosso-pharyngeal nerves were affected. As far as eye fundus was concerned, there were no particular pathological symptoms, except for a slight hyperemia.

Motor disturbances were expressed chiefly in changes of muscular tonus; there was often bending contracture of the upper extremities and unbending contracture of the lower extremities with a pronounced planta function of the foot (posture of decerebral rigidity).

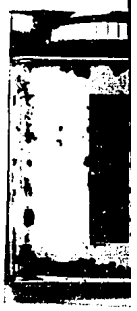
In other cases, both upper and lower extremities were in a flexed state. Increased tonicity predominated in proximal regions, and this condition was in all cases of the mixed pyramidal-extrapyramidal type. In three cases, the "midwife's hands" position was observed. In three cases, there was change of the tonus and position of the upper extremities, depending on the angle through which the head was turned, a phenomenon belonging to a type which indicates a midbrain mechanism. There were no pareses or paralyses. In some cases, hyperkinesis, athetoic position of the hands, and trembling of the extremities and tongue were observed. The tendon reflexes were increased and there was usually anisoreflexion; in the majority of cases the knee reflexes were heightened, while the Achilles tendon reflexes were absent. Abdominal reflexes were absent in practically all cases. Plantar reflexes were frequently increased and accompanied by a heightened tonic flexion of the toes. In other words, there was frequent divergence between the intensities of abdominal and plantar reflexes. Often there were pathological reflexes of the flexion-releasing type (Babinski's reflex, Oppenheim's reflex). In the majority of cases, pronounced defense reflexes, pain reflexes, and the Marie-Foix-Bekhterev symptom were present. In all cases, symptoms of oral automatism (of the snout type, nasolabial, or suction type) were observed. In 44 instances, there was a grasping reflex.

Disturbances of sensibility could not be investigated because of the serious condition of the patients. The speech was slow, monotonous, and hollow.

In the vegetative system, the following conditions were present: regional hyperemias, acrocyanosis, persistent red dermographism, increased pilomotor reflex, and a well-expressed Aschner phenomenon.

The spinal fluid was colorless and transparent in all cases. It flowed out under raised pressure. The quantity of proteins was somewhat increased (0.66%); the globulin reactions were positive, as a rule; in some cases, there was a slight cytosis (20-30 lymphocytes).

In cases of Group 2, pronounced changes of the psyche occurred. These changes were particularly noticeable during the period of convalescence, while during the acute period they were masked by disturbances of consciousness. These changes had the characteristics of a frontal syndrome. The pathological state of motor functions in this group was particularly pronounced, with especially strong impairment of the extrapyramidal system. This was expressed in hypokinesis, absence of synergetic movements of the arms in walking, cataplectic freezing in imparted positions, athetoic tendencies, trembling of fingers, and myoclonic twitchings of the face musculature. In this group, disturbances of motor coordination of the cerebellum type were especially noticeable. The neurological symptoms were dominated by these phenomena to such an extent that one might have assumed an acute



Leyden-Westphal ataxia. As far as sensibility is concerned, there was general hyperesthesia.

The patients of Group 3, just as those of Group 2, initially complained about a headache and had symptoms of a meningeal condition. However, the disease took a less severe course. As for neurological symptoms, there were disturbances of motor coordination that were expressed chiefly in atactic walking and instability in Romberg's posture. Furthermore, strengthening of radiculoneuritic symptoms was observed during the period of convalescence.

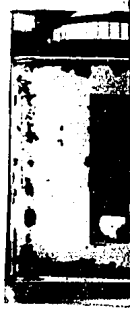
Group 4 was distinguished by a light course of the disease, absence of meningeal symptoms, and weak neurological symptoms indicating affliction of the pyramidal tract and of the radiculoneuritic section of the nervous system.

Data obtained by a catamnestic examination, extending over one year, of patients who had the disease in 1947 disclosed in some cases the presence of diffuse symptoms of an affliction of the nervous system, constant headaches, pronounced vegetative emotional instability, light pareses of nerves of the large brain, strengthening or weakening of tendon reflexes, and pathological reflexes.

Pathologo-anatomical investigations disclosed a pronounced hyperemia of brain membranes and the brain substance, in some cases subarachnoidal hemorrhages, extended hemorrhages into the gastro-intestinal tract (submucous hematomata of the stomach), hemorrhages into the lung tissue and the spleen capsule, and degenerative changes of internal organs.

Microscopic examination showed in all cases oedema of the pia mater and loosening of the connective fibers. There is an acute state of excessive filling of vessels of this membrane with blood, and, in some cases, hemorrhages into membranes and pronounced infiltration are observed. Blood vessels in the large brain and the brain stem are extended and filled to excess with blood. They also contain stases. Around capillaries and precapillaries there are diapedetic hemorrhages. In addition to hemorrhages, plasmorrhages (accumulations of oedematous liquid) are observed. The walls of blood vessels are oedematous, with swollen endothelium. Occasionally, there is proliferation of blood vessel endothelium with subsequent desquamation. In the intraadventitial spaces of blood vessels, particularly those of the brain stem, there is light lymphocytic infiltration. Diffuse proliferation of micro- and oligo-dendroglia is noticeable, and the glia around vessels frequently contracts, forming loosened knots. In astrocytes, there are degenerative changes of irregular shape; more pronounced are degenerative changes of microglia cells. Nerve cells are comparatively unaffected. However, in almost all cases we were able to detect either an acute swelling of these cells or ischemic, sometimes perivascular, impairment of them. A diffuse pathological process affects the whole brain. However, the strongest changes are noticeable in the middle brain, the pons varioli, and after this in the putamen, visual bulge, and, finally, in the brain cortex. In other words, Bukovina hemorrhagic fever is essentially a diffuse hemorrhagic capillarotoxicosis involving elements of an exudative-proliferative process.

On summarizing our data, we see that the clinical aspects of the affliction of the nervous system in Bukovina hemorrhagic fever are characterized by the following conditions: disturbances of consciousness; meningeal symptoms; affection of the brain nerves of the oculomotor and bulbar groups; motor disturbances, particularly disturbances of muscle tonus of the pyramidal as well as extrapyramidal type, hyperkineses, disturbed reflexes; disturbed coordination of the cerebellum type; oral automatism reflexes, tonic reflexes affecting the neck, grasping reflex; vegetative pathology. This clinical multiplicity of symptoms indicating affection of the cortex, subcortical ganglia, and the brain axis is satisfactorily explained by pathological data, which disclose a diffuse process.



One must emphasize the shallow, unstable, and reversible character of the clinical symptoms, as well as the absence of symptoms indicating spinal pathology.

All these data permit one to distinguish between cases of hemorrhagic fever and those of tick encephalitis, which also occur in the wooded regions of Bukovina. The clinical picture of Bukovina tick encephalitis is extremely multifarious: stem myelitic, myeloradiculoneuritic forms, and forms with predominant affection of the radiculoneuritic section of the nervous system were observed. However, in all cases of Bukovina tick encephalitis, there were clear symptoms of affection of the gray as well as white matter of both the brain and the spine, which was clinically expressed in pareses and atrophies in the cervico-clavical region. No such indications were present in our clinical material. However, upon comparing the clinical picture of affection of the nervous system in Bukovina hemorrhagic fever with that in Crimean hemorrhagic fever, we must stress the much greater intensity and stability of neurological symptoms in Bukovina hemorrhagic fever. This may be connected with a more pronounced neurotropic quality of the virus of the disease under discussion.

According to Shutova's data, the neurological symptoms in Crimean hemorrhagic fever basically indicate an affection of the vegetative nervous system; symptoms of affection of the somatic nervous system are indistinctly expressed and bear a transient character (there are light disturbances of consciousness, weakly expressed meningeal symptoms, unstable pyramidal and extrapyramidal disturbances). In our acute cases, we observed a syndrome of diffuse meningoencephalitis with pronounced symptoms of the decerebral rigidity and tonic neck reflex type, i. e., symptoms connected with elimination of the functions of the brain cortex, of pyramidal as well as extrapyramidal tracts. The neurological syndrome in our acute cases is almost identical with that of Japanese mosquito encephalitis: only virusological investigations permit a differentiation of these two diseases. Furthermore, in our cases, relatively stable residual symptoms of disturbed psyche, as well as pathological symptoms of the extrapyramidal and cerebellum type, were present. All this is not observed in Crimean hemorrhagic fever.

The typical traits outlined above lead to the conclusion that the disease which was observed in Bukovina bears a distinct and independent character.

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